Rx Delivery Systems in Pipeline for Depression, ED

BY CARL SHERMAN
Contributing Writer

NEW YORK — Two new transdermal and intranasal drug delivery systems, for which approval is foreseeable, may have utility in treating depression and erectile dysfunction, Donald S. Robinson, M.D., said at a meeting on psychopharmacology sponsored by New York University.

Oral administration delays onset of action since the drug passes through the digestive tract and is absorbed in the small bowel. Moreover, when the drug enters the body via this route, it undergoes first-pass metabolism in the liver.

Often, a large dose must be taken to get a relatively small amount to the site of action, noted Dr. Robinson, a psychiatrist and pharmaceutical consultant in Melbourne, Fla.

Parenteral administration boosts bioavailability. Far more of the drug goes directly into central systemic circulation, which favors the brain, so a proportionally greater amount will be delivered to the central nervous system than to other organs. Avoiding first-pass metabolism in the liver prevents production of metabolites that can alter a drug's safety and side effect profile, said Dr. Robinson, a member of the board of directors of Pherin Pharmaceuticals and a vice president at Bristol-Myers Squibb.

Transdermal and intranasal formulations have promise for routine use. Transdermal selegiline may make it possible to achieve the antidepressant efficacy of a monoamine oxidase inhibitor without the dietary restrictions and acute hypertensive risks that have been largely responsible for the fall from favor of this drug class, Dr. Robinson said.

Conventional MAO inhibitors interfere with the action of an isoenzyme, MAO-A, that normally prevents the absorption of tyramine, a food component that can raise blood pressure dramatically, he said.

Although the MAO inhibitor selegiline is selective at low doses for MAO-B receptors, given in oral doses that achieve an antidepressant effect it loses its selectivity, inhibiting both MAO-A and MAO-B and arousing the same safety issues as with other MAO inhibitors.

The transdermal delivery route obviates this problem: The drug enters systemic circulation directly, so a therapeutic level is achieved in the brain at a dose that spares MAO-A receptors in the intestine, Dr. Robinson said.

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Three placebo-controlled trials showed the efficacy of transdermal selegiline in major depression, and a 2-year trial found it to reduce relapse by half, he said.

"In all the clinical trials [in which more than 2,000 individuals were exposed to the drug] there was not a single episode of acute hypertensive crisis, although there were no dietary restrictions after the first trial," he said. The formulation is expected to be marketed later this year by Bristol-Myers Squibb and Somerset Pharmaceuticals, Dr. Robinson said.

Intrasnasal delivery may allow the use of a novel drug for erectile dysfunction. PT-141, a synthetic peptide under development by Palatin Technologies, operates through a different mechanism than existing erectile dysfunction drugs such as sildenafil (Viagra): It acts centrally, not peripherally, he said.

Because the peptide is a large molecule, it cannot pass unaltered through the digestive system, but it is well absorbed nasally.

The rapid action of the drug when administered in a nasal spray—high blood levels are achieved within 10-15 minutes—allows superior flexibility in timing, Dr. Robinson said.

In a phase IIb clinical trial, 271 sildenafil-responsive men with erectile dysfunction (some with organic causes including diabetes and hypertension) were randomized to receive PT-141 or placebo. Changes in scores on the International Index of Erectile Dysfunction, a self-rating scale, were significantly greater with the drug than with placebo at three of the four doses tested.

"It looks like this drug will be available within 2-3 years," Dr. Robinson said. Phase III trials are planned for late 2006, according to the Palatin Technologies Web site. ■